

WO 2005/089445

1/22

PCT/US2005/008960

10/593466

<110> SZKUDLINSI, Mariusz W.  
WIENTRAUB, Bruce D.

<120> Follicle Stimulating Hormone Superagonists

<130> 056815-5001-WO

<150> US 60/554,419

<151> 2004-03-19

<160> 24

<170> PatentIn version 3.3

<210> 1

<211> 92

<212> PRT

<213> Homo sapiens

<400> 1

Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr Leu Gln Glu Asn Pro  
1 5 10 15

Phe Phe Ser Gln Pro Gly Ala Pro Ile Leu Gln Cys Met Gly Cys Cys  
20 25 30

Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser Lys Lys Thr Met Leu  
35 40 45

Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys Cys Val Ala Lys Ser  
50 55 60

Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys Val Glu Asn His Thr  
65 70 75 80

Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys Ser  
85 90

<210> 2

<211> 111

<212> PRT

<213> Homo sapiens

<400> 2

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu  
1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys  
20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln  
35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro  
50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr  
65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val  
85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu  
100 105 110

<210> 3

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino terminal extension; potential glycosylation recognition site

<400> 3

Ala Asn Ile Thr Val  
1 5

<210> 4

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino terminal extension; potential glycosylation recognition site

<400> 4

Ala Asn Ile Thr Val Asn Ile Thr Val  
1 5

<210> 5

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Negatively charged amino acid insert to modify protein half-life

<400> 5

Gly Glu Phe Thr  
1

<210> 6  
<211> 5  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Negatively charged amino acid insert to modify protein half-life  
<400> 6

Gly Glu Phe Thr Thr  
1 5

<210> 7  
<211> 11  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> FSH segment with negatively charged amino acid insert to modify protein half-life  
<400> 7

Ala Asp Pro Gly Glu Phe Thr Val Gln Asp Cys  
1 5 10

<210> 8  
<211> 11  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> FSH segment with negatively charged amino acid insert to modify protein half-life  
<400> 8

Ala Asp Pro Gly Glu Phe Thr Thr Gln Asp Cys  
1 5 10

<210> 9  
<211> 97  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Mutated FSH alpha mature peptide sequence with N-terminal extension  
<400> 9

Ala Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr  
1 5 10 15

4/22

Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala Pro Ile Leu Gln  
 20 25 30

Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser  
 35 40 45

Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys  
 50 55 60

Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys  
 65 70 75 80

Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys  
 85 90 95

Ser

<210> 10

<211> 97

<212> PRT

<213> Artificial Sequence

<220>

<223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 10

Ala Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr  
 1 5 10 15

Leu Gln Arg Asn Pro Phe Phe Ser Arg Pro Gly Ala Pro Ile Leu Gln  
 20 25 30

Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser  
 35 40 45

Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys  
 50 55 60

Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Arg Phe Lys  
 65 70 75 80

Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys  
 85 90 95

Ser

<210> 11  
 <211> 101  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 11

Ala Asn Ile Thr Val Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys  
 1 5 10 15

Pro Glu Cys Thr Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala  
 20 25 30

Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr  
 35 40 45

Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser  
 50 55 60

Glu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met  
 65 70 75 80

Gly Gly Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys  
 85 90 95

Tyr Tyr His Lys Ser  
 100

<210> 12  
 <211> 101  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 12

Ala Asn Ile Thr Val Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys  
 1 5 10 15

Pro Glu Cys Thr Leu Gln Arg Asn Pro Phe Phe Ser Arg Pro Gly Ala  
 20 25 30

6/22

Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr  
 35 40 45

Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser  
 50 55 60

Glu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met  
 65 70 75 80

Gly Arg Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys  
 85 90 95

Tyr Tyr His Lys Ser  
 100

<210> 13  
 <211> 111  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Mutated FSH beta mature peptide sequence

<400> 13

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu  
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys  
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln  
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro  
 50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Asn Ala Thr  
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val  
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu  
 100 105 110

<210> 14  
 <211> 111

7/22

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Mutated FSH beta mature peptide sequence

&lt;400&gt; 14

Asn Ser Cys Arg Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu  
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys  
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln  
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro  
 50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Asn Ala Thr  
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val  
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu  
 100 105 110

&lt;210&gt; 15

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Mutated FSH beta mature peptide sequence

&lt;400&gt; 15

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu  
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys  
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln  
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Asn Glu Thr Val Arg Val Pro  
 50 55 60

8/22

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr  
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val  
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu  
 100 105 110

<210> 16  
 <211> 111  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Mutated FSH beta mature peptide sequence

<400> 16

Asn Ser Cys Arg Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu  
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys  
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln  
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Asn Glu Thr Val Arg Val Pro  
 50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr  
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val  
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu  
 100 105 110

<210> 17  
 <211> 121  
 <212> PRT  
 <213> Homo sapiens

<400> 17

Ser Arg Glu Pro Leu Arg Pro Trp Cys His Pro Ile Asn Ala Ile Leu  
 1 5 10 15



9/22

Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr Val Asn Thr Thr  
                   20                                  25                                  30

Ile Cys Ala Gly Tyr Cys Pro Thr Met Met Arg Val Leu Gln Ala Val  
                   35                                  40                                  45

Leu Pro Pro Leu Pro Gln Val Val Cys Thr Tyr Arg Asp Val Arg Phe  
                   50                                  55                                  60

Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val Asp Pro Val Val  
                   65                                  70                                  75                                  80

Ser Phe Pro Val Ala Leu Ser Cys Arg Cys Gly Pro Cys Arg Arg Ser  
                                   85                                  90                                  95

Thr Ser Asp Cys Gly Gly Pro Lys Asp His Pro Leu Thr Cys Asp His  
                   100                                  105                                  110

Pro Gln Leu Ser Gly Leu Leu Phe Leu  
                   115                                  120

<210> 18  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 18

Met Asp Tyr Tyr Arg Lys Tyr Ala Ala Ile Phe Leu Val Thr Leu Ser  
   1                                  5                                  10                                  15

Val Phe Leu His Val Leu His Ser  
                   20

<210> 19  
 <211> 18  
 <212> PRT  
 <213> Homo sapiens

<400> 19

Met Lys Thr Leu Gln Phe Phe Phe Leu Phe Cys Cys Trp Lys Ala Ile  
   1                                  5                                  10                                  15

Cys Cys

<210> 20  
 <211> 20

<211> PRT  
 <213> Homo sapiens

<400> 20

Met Glu Met Leu Gln Gly Leu Leu Leu Leu Leu Leu Ser Met Gly  
 1 5 10 15

Gly Ala Trp Ala  
 20

<210> 21  
 <211> 692  
 <212> PRT  
 <213> Rattus norvegicus

<400> 21

Met Ala Leu Leu Leu Val Ser Leu Leu Ala Phe Leu Gly Thr Gly Ser  
 1 5 10 15

Gly Cys His His Trp Leu Cys His Cys Ser Asn Arg Val Phe Leu Cys  
 20 25 30

Gln Asp Ser Lys Val Thr Glu Ile Pro Thr Asp Leu Pro Arg Asn Ala  
 35 40 45

Ile Glu Leu Arg Phe Val Leu Thr Lys Leu Arg Val Ile Pro Lys Gly  
 50 55 60

Ser Phe Ala Gly Phe Gly Asp Leu Glu Lys Ile Glu Ile Ser Gln Asn  
 65 70 75 80

Asp Val Leu Glu Val Ile Glu Ala Asp Val Phe Ser Asn Leu Pro Lys  
 85 90 95

Leu His Glu Ile Arg Ile Glu Lys Ala Asn Asn Leu Leu Tyr Ile Asn  
 100 105 110

Pro Glu Ala Phe Gln Asn Leu Pro Ser Leu Arg Tyr Leu Leu Ile Ser  
 115 120 125

Asn Thr Gly Ile Lys His Leu Pro Ala Val His Lys Ile Gln Ser Leu  
 130 135 140

Gln Lys Val Leu Leu Asp Ile Gln Asp Asn Ile Asn Ile His Ile Val  
 145 150 155 160

Ala Arg Asn Ser Phe Met Gly Leu Ser Phe Glu Ser Val Ile Leu Trp

|  |     |     |
|--|-----|-----|
| 165  | 170 | 175 |
| Leu Ser Lys Asn Gly Ile Glu Glu Ile His Asn Cys Ala Phe Asn Gly<br>180 185 190     |     |     |
| Thr Gln Leu Asp Glu Leu Asn Leu Ser Asp Asn Asn Asn Leu Glu Glu<br>195 200 205     |     |     |
| Leu Pro Asn Asp Val Phe Gln Gly Ala Ser Gly Pro Val Ile Leu Asp<br>210 215 220     |     |     |
| Ile Ser Arg Thr Lys Val His Ser Leu Pro Asn His Gly Leu Glu Asn<br>225 230 235 240 |     |     |
| Leu Lys Lys Leu Arg Ala Arg Ser Thr Tyr Arg Leu Lys Lys Leu Pro<br>245 250 255     |     |     |
| Asn Leu Asp Lys Phe Val Thr Leu Met Glu Ala Ser Leu Thr Tyr Pro<br>260 265 270     |     |     |
| Ser His Cys Cys Ala Phe Ala Asn Leu Lys Arg Gln Ile Ser Glu Leu<br>275 280 285     |     |     |
| His Pro Ile Cys Asn Lys Ser Ile Leu Arg Gln Asp Ile Asp Asp Met<br>290 295 300     |     |     |
| Thr Gln Ile Gly Asp Gln Arg Val Ser Leu Ile Asp Asp Glu Pro Ser<br>305 310 315 320 |     |     |
| Tyr Gly Lys Gly Ser Asp Met Met Tyr Asn Glu Phe Asp Tyr Asp Leu<br>325 330 335     |     |     |
| Cys Asn Glu Val Val Asp Val Thr Cys Ser Pro Lys Pro Asp Ala Phe<br>340 345 350     |     |     |
| Asn Pro Cys Glu Asp Ile Met Gly Tyr Asn Ile Leu Arg Val Leu Ile<br>355 360 365     |     |     |
| Trp Phe Ile Ser Ile Leu Ala Ile Thr Gly Asn Thr Thr Val Leu Val<br>370 375 380     |     |     |
| Val Leu Thr Thr Ser Gln Tyr Lys Leu Thr Val Pro Arg Phe Leu Met<br>385 390 395 400 |     |     |
| Cys Asn Leu Ala Phe Ala Asp Leu Cys Ile Gly Ile Tyr Leu Leu Leu<br>405 410 415     |     |     |

12/22

Ile Ala Ser Val Asp Ile His Thr Lys Ser Gln Tyr His Asn Tyr Ala  
 420 425 430

Ile Asp Trp Gln Thr Gly Ala Gly Cys Asp Ala Ala Gly Phe Phe Thr  
 435 440 445

Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Ala Ile Thr Leu  
 450 455 460

Glu Arg Trp His Thr Ile Thr His Ala Met Gln Leu Glu Cys Lys Val  
 465 470 475 480

Gln Leu Arg His Ala Ala Ser Val Met Val Leu Gly Trp Thr Phe Ala  
 485 490 495

Phe Ala Ala Ala Leu Phe Pro Ile Phe Gly Ile Ser Ser Tyr Met Lys  
 500 505 510

Val Ser Ile Cys Leu Pro Met Asp Ile Asp Ser Pro Leu Ser Gln Leu  
 515 520 525

Tyr Val Met Ala Leu Leu Val Leu Asn Val Leu Ala Phe Val Val Ile  
 530 535 540

Cys Gly Cys Tyr Thr His Ile Tyr Leu Thr Val Arg Asn Pro Thr Ile  
 545 550 555 560

Val Ser Ser Ser Ser Asp Thr Lys Ile Ala Lys Arg Met Ala Thr Leu  
 565 570 575

Ile Phe Thr Asp Phe Leu Cys Met Ala Pro Ile Ser Phe Phe Ala Ile  
 580 585 590

Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala Lys Ile  
 595 600 605

Leu Leu Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu  
 610 615 620

Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile Leu Leu  
 625 630 635 640

Ser Lys Phe Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg Thr Glu  
 645 650 655

13/22

Thr Ser Ser Ala Thr His Asn Phe His Ala Arg Lys Ser His Cys Ser  
 660 665 670

Ser Ala Pro Arg Val Thr Asn Ser Tyr Val Leu Val Pro Leu Asn His  
 675 680 685

Ser Ser Gln Asn  
 690

<210> 22  
 <211> 695  
 <212> PRT  
 <213> Homo sapiens

<400> 22

Met Ala Leu Leu Leu Val Ser Leu Leu Ala Phe Leu Ser Leu Gly Ser  
 1 5 10 15

Gly Cys His His Arg Ile Cys His Cys Ser Asn Arg Val Phe Leu Cys  
 20 25 30

Gln Glu Ser Lys Val Thr Glu Ile Pro Ser Asp Leu Pro Arg Asn Ala  
 35 40 45

Ile Glu Leu Arg Phe Val Leu Thr Lys Leu Arg Val Ile Gln Lys Gly  
 50 55 60

Ala Phe Ser Gly Phe Gly Asp Leu Glu Lys Ile Glu Ile Ser Gln Asn  
 65 70 75 80

Asp Val Leu Glu Val Ile Glu Ala Asp Val Phe Ser Asn Leu Pro Lys  
 85 90 95

Leu His Glu Ile Arg Ile Glu Lys Ala Asn Asn Leu Leu Tyr Ile Thr  
 100 105 110

Pro Glu Ala Phe Gln Asn Leu Pro Asn Leu Gln Tyr Leu Leu Ile Ser  
 115 120 125

Asn Thr Gly Ile Lys His Leu Pro Asp Val His Lys Ile His Ser Leu  
 130 135 140

Gln Lys Val Leu Leu Asp Ile Gln Asp Asn Ile Asn Ile His Thr Ile  
 145 150 155 160

Glu Arg Asn Ser Phe Val Gly Leu Ser Phe Glu Ser Val Ile Leu Trp

165

170

175

Met Cys Asn Leu Ala Phe Ala Asp Leu Cys Ile Gly Ile Tyr Leu Leu  
405 410 415

15/22

Leu Ile Ala Ser Val Asp Ile His Thr Lys Ser Gln Tyr His Asn Tyr  
420 425 430

Ala Ile Asp Trp Gln Thr Gly Ala Gly Cys Asp Ala Ala Gly Phe Phe  
435 440 445

Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Ala Ile Thr  
450 455 460

Leu Glu Arg Trp His Thr Ile Thr His Ala Met Gln Leu Asp Cys Lys  
465 470 475 480

Val Gln Leu Arg His Ala Ala Ser Val Met Val Met Gly Trp Ile Phe  
485 490 495

Ala Phe Ala Ala Ala Leu Phe Pro Ile Phe Gly Ile Ser Ser Tyr Met  
500 505 510

Lys Val Ser Ile Cys Leu Pro Met Asp Ile Asp Ser Pro Leu Ser Gln  
515 520 525

Leu Tyr Val Met Ser Leu Leu Val Leu Asn Val Leu Ala Phe Val Val  
530 535 540

Ile Cys Gly Cys Tyr Ile His Ile Tyr Leu Thr Val Arg Asn Pro Asn  
545 550 555 560

Ile Val Ser Ser Ser Ser Asp Thr Arg Ile Ala Lys Arg Met Ala Met  
565 570 575

Leu Ile Phe Thr Asp Phe Leu Cys Met Ala Pro Ile Ser Phe Phe Ala  
580 585 590

Ile Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala Lys  
595 600 605

Ile Leu Leu Val Leu Phe His Pro Ile Asn Ser Cys Ala Asn Pro Phe  
610 615 620

Leu Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile Leu  
625 630 635 640

Leu Ser Lys Cys Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg Thr  
645 650 655

16/22

Glu Thr Ser Ser Thr Val His Asn Thr His Pro Arg Asn Gly His Cys  
                   660                                  665                                  670

Ser Ser Ala Pro Arg Val Thr Ser Gly Ser Thr Tyr Ile Leu Val Pro  
           675                                  680                                  685

Leu Ser His Leu Ala Gln Asn  
       690                                  695

<210> 23  
 <211> 700  
 <212> PRT  
 <213> Rattus sp.

<400> 23

Met Gly Arg Arg Val Pro Ala Leu Arg Gln Leu Leu Val Leu Ala Val  
 1                                  5                                  10                                  15

Leu Leu Leu Lys Pro Ser Gln Leu Gln Ser Arg Glu Leu Ser Gly Ser  
                   20                                  25                                  30

Arg Cys Pro Glu Pro Cys Asp Cys Ala Pro Asp Gly Ala Leu Arg Cys  
           35                                  40                                  45

Pro Gly Pro Arg Ala Gly Leu Ala Arg Leu Ser Leu Thr Tyr Leu Pro  
       50                                  55                                  60

Val Lys Val Ile Pro Ser Gln Ala Phe Arg Gly Leu Asn Glu Val Val  
 65                                  70                                  75                                  80

Lys Ile Glu Ile Ser Gln Ser Asp Ser Leu Glu Arg Ile Glu Ala Asn  
                   85                                  90                                  95

Ala Phe Asp Asn Leu Leu Asn Leu Ser Glu Leu Leu Ile Gln Asn Thr  
           100                                  105                                  110

Lys Asn Leu Leu Tyr Ile Glu Pro Gly Ala Phe Thr Asn Leu Pro Arg  
           115                                  120                                  125

Leu Lys Tyr Leu Ser Ile Cys Asn Thr Gly Ile Arg Thr Leu Pro Asp  
       130                                  135                                  140

Val Thr Lys Ile Ser Ser Ser Glu Phe Asn Phe Ile Leu Glu Ile Cys  
 145                                  150                                  155                                  160

Asp Asn Leu His Ile Thr Thr Ile Pro Gly Asn Ala Phe Gln Gly Met



| 165 |     |     |     |     |     |     |     |     |     | 170 |     |     |     |     | 175 |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|
| Asn | Asn | Glu | Ser | Val | Thr | Leu | Lys | Leu | Tyr | Gly | Asn | Gly | Phe | Glu | Glu |  |  |  |  |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |  |  |  |
| Val | Gln | Ser | His | Ala | Phe | Asn | Gly | Thr | Thr | Leu | Ile | Ser | Leu | Glu | Leu |  |  |  |  |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |  |  |  |
| Lys | Glu | Asn | Ile | Tyr | Leu | Glu | Lys | Met | His | Ser | Gly | Ala | Phe | Gln | Gly |  |  |  |  |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |  |  |  |
| Ala | Thr | Gly | Pro | Ser | Ile | Leu | Asp | Ile | Ser | Ser | Thr | Lys | Leu | Gln | Ala |  |  |  |  |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |  |  |  |
| Leu | Pro | Ser | His | Gly | Leu | Glu | Ser | Ile | Gln | Thr | Leu | Ile | Ala | Leu | Ser |  |  |  |  |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |  |  |  |
| Ser | Tyr | Ser | Leu | Lys | Thr | Leu | Pro | Ser | Lys | Glu | Lys | Phe | Thr | Ser | Leu |  |  |  |  |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |  |  |  |
| Leu | Val | Ala | Thr | Leu | Thr | Tyr | Pro | Ser | His | Cys | Cys | Ala | Phe | Arg | Asn |  |  |  |  |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |  |  |  |
| Leu | Pro | Lys | Lys | Glu | Gln | Asn | Phe | Ser | Phe | Ser | Ile | Phe | Glu | Asn | Phe |  |  |  |  |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |  |  |  |
| Ser | Lys | Gln | Cys | Glu | Ser | Thr | Val | Arg | Lys | Ala | Asp | Asn | Glu | Thr | Leu |  |  |  |  |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |  |  |  |
| Tyr | Ser | Ala | Ile | Phe | Glu | Glu | Asn | Glu | Leu | Ser | Gly | Trp | Asp | Tyr | Asp |  |  |  |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |  |  |  |
| Tyr | Gly | Phe | Cys | Ser | Pro | Lys | Thr | Leu | Gln | Cys | Ala | Pro | Glu | Pro | Asp |  |  |  |  |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |  |  |  |
| Ala | Phe | Asn | Pro | Cys | Glu | Asp | Ile | Met | Gly | Tyr | Ala | Phe | Leu | Arg | Val |  |  |  |  |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |  |  |  |
| Leu | Ile | Trp | Leu | Ile | Asn | Ile | Leu | Ala | Ile | Phe | Gly | Asn | Leu | Thr | Val |  |  |  |  |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |  |  |  |
| Leu | Phe | Val | Leu | Leu | Thr | Ser | Arg | Tyr | Lys | Leu | Thr | Val | Pro | Arg | Phe |  |  |  |  |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |  |  |  |
| Leu | Met | Cys | Asn | Leu | Ser | Phe | Ala | Asp | Phe | Cys | Met | Gly | Leu | Tyr | Leu |  |  |  |  |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |  |  |  |  |

Leu Leu Ile Ala Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn  
 420 425 430

His Ala Ile Asp Trp Gln Thr Gly Ser Gly Cys Gly Ala Ala Gly Phe  
 435 440 445

Phe Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile  
 450 455 460

Thr Leu Glu Arg Trp His Thr Ile Thr Tyr Ala Val Gln Leu Asp Gln  
 465 470 475 480

Lys Leu Arg Leu Arg His Ala Ile Pro Ile Met Leu Gly Gly Trp Leu  
 485 490 495

Phe Ser Thr Leu Ile Ala Thr Met Pro Leu Val Gly Ile Ser Asn Tyr  
 500 505 510

Met Lys Val Ser Ile Cys Leu Pro Met Asp Val Glu Ser Thr Leu Ser  
 515 520 525

Gln Val Tyr Ile Leu Ser Ile Leu Ile Leu Asn Val Val Ala Phe Val  
 530 535 540

Val Ile Cys Ala Cys Tyr Ile Arg Ile Tyr Phe Ala Val Gln Asn Pro  
 545 550 555 560

Glu Leu Thr Ala Pro Asn Lys Asp Thr Lys Ile Ala Lys Lys Met Ala  
 565 570 575

Ile Leu Ile Phe Thr Asp Phe Thr Cys Met Ala Pro Ile Ser Phe Phe  
 580 585 590

Ala Ile Ser Ala Ala Phe Lys Val Pro Leu Ile Thr Val Thr Asn Ser  
 595 600 605

Lys Ile Leu Leu Val Leu Phe Tyr Pro Val Asn Ser Cys Ala Asn Pro  
 610 615 620

Phe Leu Tyr Ala Ile Phe Thr Lys Ala Phe Gln Arg Asp Phe Leu Leu  
 625 630 635 640

Leu Leu Ser Arg Phe Gly Cys Cys Lys Arg Arg Ala Glu Leu Tyr Arg  
 645 650 655

19/22

Arg Lys Glu Phe Ser Ala Tyr Thr Ser Asn Cys Lys Asn Gly Phe Pro  
                   660                                  665                                  670

Gly Ala Ser Lys Pro Ser Gln Ala Thr Leu Lys Leu Ser Thr Val His  
                   675                                  680                                  685

Cys Gln Gln Pro Ile Pro Pro Arg Ala Leu Thr His  
                   690                                  695                                  700

<210> 24  
 <211> 699  
 <212> PRT  
 <213> Homo sapiens

<400> 24

Met Lys Gln Arg Phe Ser Ala Leu Gln Leu Leu Lys Leu Leu Leu Leu  
 1                                  5                                  10                                  15

Leu Gln Pro Pro Leu Pro Arg Ala Leu Arg Glu Ala Leu Cys Pro Glu  
                   20                                  25                                  30

Pro Cys Asn Cys Val Pro Asp Gly Ala Leu Arg Cys Pro Gly Pro Thr  
                   35                                  40                                  45

Ala Gly Leu Thr Arg Leu Ser Leu Ala Tyr Leu Pro Val Lys Val Ile  
                   50                                  55                                  60

Pro Ser Gln Ala Phe Arg Gly Leu Asn Glu Val Ile Lys Ile Glu Ile  
 65                                  70                                  75                                  80

Ser Gln Ile Asp Ser Leu Glu Arg Ile Glu Ala Asn Ala Phe Asp Asn  
                   85                                  90                                  95

Leu Leu Asn Leu Ser Glu Ile Leu Ile Gln Asn Thr Lys Asn Leu Arg  
                   100                                  105                                  110

Tyr Ile Glu Pro Gly Ala Phe Ile Asn Leu Pro Gly Leu Lys Tyr Leu  
                   115                                  120                                  125

Ser Ile Cys Asn Thr Gly Ile Arg Lys Phe Pro Asp Val Thr Lys Val  
                   130                                  135                                  140

Phe Ser Ser Glu Ser Asn Phe Ile Leu Glu Ile Cys Asp Asn Leu His  
 145                                  150                                  155                                  160

Ile Thr Thr Ile Pro Gly Asn Ala Phe Gln Gly Met Asn Asn Glu Ser

|   |     |  |     |  |     |
|---|-----|--|-----|--|-----|
|   | 165 |  | 170 |  | 175 |
| Val Thr Leu Lys Leu Tyr Gly Asn Gly Phe Glu Glu Val Gln Ser His | 180 |  | 185 |  | 190 |
| Ala Phe Asn Gly Thr Thr Leu Thr Ser Leu Glu Leu Lys Glu Asn Val | 195 |  | 200 |  | 205 |
| His Leu Glu Lys Met His Asn Gly Ala Phe Arg Gly Ala Thr Gly Pro | 210 |  | 215 |  | 220 |
| Lys Thr Leu Asp Ile Ser Ser Thr Lys Leu Gln Ala Leu Pro Ser Tyr | 225 |  | 230 |  | 235 |
| Gly Leu Glu Ser Ile Gln Arg Leu Ile Ala Thr Ser Ser Tyr Ser Leu | 245 |  | 250 |  | 255 |
| Lys Lys Leu Pro Ser Arg Glu Thr Phe Val Asn Leu Leu Glu Ala Thr | 260 |  | 265 |  | 270 |
| Leu Thr Tyr Pro Ser His Cys Cys Ala Phe Arg Asn Leu Pro Thr Lys | 275 |  | 280 |  | 285 |
| Glu Gln Asn Phe Ser His Ser Ile Ser Glu Asn Phe Ser Lys Gln Cys | 290 |  | 295 |  | 300 |
| Glu Ser Thr Val Arg Lys Val Ser Asn Lys Thr Leu Tyr Ser Ser Met | 305 |  | 310 |  | 315 |
| Leu Ala Glu Ser Glu Leu Ser Gly Trp Asp Tyr Glu Tyr Gly Phe Cys | 325 |  | 330 |  | 335 |
| Leu Pro Lys Thr Pro Arg Cys Ala Pro Glu Pro Asp Ala Phe Asn Pro | 340 |  | 345 |  | 350 |
| Cys Glu Asp Ile Met Gly Tyr Asp Phe Leu Arg Val Leu Ile Trp Leu | 355 |  | 360 |  | 365 |
| Ile Asn Ile Leu Ala Ile Met Gly Asn Met Thr Val Leu Phe Val Leu | 370 |  | 375 |  | 380 |
| Leu Thr Ser Arg Tyr Lys Leu Thr Val Pro Arg Phe Leu Met Cys Asn | 385 |  | 390 |  | 395 |
| Leu Ser Phe Ala Asp Phe Cys Met Gly Leu Tyr Leu Leu Leu Ile Ala | 405 |  | 410 |  | 415 |

Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn His Ala Ile Asp  
 420 425 430

Trp Gln Thr Gly Ser Gly Cys Ser Thr Ala Gly Phe Phe Thr Val Phe  
 435 440 445

Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile Thr Leu Glu Arg  
 450 455 460

Trp His Thr Ile Thr Tyr Ala Ile His Leu Asp Gln Lys Leu Arg Leu  
 465 470 475 480

Arg His Ala Ile Leu Ile Met Leu Gly Gly Trp Leu Phe Ser Ser Leu  
 485 490 495

Ile Ala Met Leu Pro Leu Val Gly Val Ser Asn Tyr Met Lys Val Ser  
 500 505 510

Ile Cys Phe Pro Met Asp Val Glu Thr Thr Leu Ser Gln Val Tyr Ile  
 515 520 525

Leu Thr Ile Leu Ile Leu Asn Val Val Ala Phe Phe Ile Ile Cys Ala  
 530 535 540

Cys Tyr Ile Lys Ile Tyr Phe Ala Val Arg Asn Pro Glu Leu Met Ala  
 545 550 555 560

Thr Asn Lys Asp Thr Lys Ile Ala Lys Lys Met Ala Ile Leu Ile Phe  
 565 570 575

Thr Asp Phe Thr Cys Met Ala Pro Ile Ser Phe Phe Ala Ile Ser Ala  
 580 585 590

Ala Phe Lys Val Pro Leu Ile Thr Val Thr Asn Ser Lys Val Leu Leu  
 595 600 605

Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu Tyr Ala  
 610 615 620

Ile Phe Thr Lys Thr Phe Gln Arg Asp Phe Phe Leu Leu Leu Ser Lys  
 625 630 635 640

Phe Gly Cys Cys Lys Arg Arg Ala Glu Leu Tyr Arg Arg Lys Asp Phe  
 645 650 655

Ser Ala Tyr Thr Ser Asn Cys Lys Asn Gly Phe Thr Gly Ser Asn Lys  
660 665 670

Pro Ser Gln Ser Thr Leu Lys Leu Ser Thr Leu His Cys Gln Gly Thr  
675 680 685

Ala Leu Leu Asp Lys Thr Arg Tyr Thr Glu Cys  
690 695